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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: John B. Harley

SERIAL NO: 07/867,819

FILING DATE: April 13, 1992

FOR: ASSAYS AND TREATMENTS FOR AUTOIMMUNE DISEASES

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

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The claimed invention is a process to identify etiologic or antigenic agents responsible for the production of autoantibodies which characterize autoimmune diseases (e.g., SLE) and compositions derived from those etiologic or antigenic agents.

The disclosed process for determining etiologic or immunogenic agents includes the following elements:

1) identifying an antigen bound by a population of autoantibodies;

2) identifying amino acid sequences within the antigen

that react with the autoantibodies (the "reactive antigenic sequences");

3) comparing the reactive antigenic sequences with amino acid sequences of other proteins to identify potential immunogens; and

4) identifying proteins that contain the greatest number of homologous amino acid sequences that correlate with the antigenic sequences reactive with autoantibodies.

As discussed in the Background of the Invention, the disclosed methodology can be used to identify etiologic agents and specific antigenic sequences involved in the expression of particular autoimmune diseases. The identity of such sequences allows those skilled in the art to design assays and reagents for the diagnosis and treatment of patients either infected with the etiologic agent or expressing antibodies to the agent. The animal model described can allow scientists to test these new therapies in an animal model before attempting to apply them to patients.

Pursuant to the duty of disclosure under 37 C.F.R. §1.56, applicant cites the following publications of which he is aware regarding prior art in assays and reagents designed for the detection and treatment of specific autoimmune diseases, animal models expressing human autoantibodies in their circulation, and the identification of etiologic agents of autoimmune diseases.

U.S. Patent No.	Patentee
4,865,970	N. Brot, K. Elkon, S.M. Skelly, H. Weissbach

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Publications

Ferris and Donaldson, Veterinary Microbiology Vol. 18, No. 3-4, pp. 243-258 (1988).

Mosier, et al., Nature Vol. 335, pp. 256-259 (1988).

Dickey, Human autoantibody producing grafts in SCID mice, presented to the Oklahoma Lupus Association, Inc., September 1, 1989.

Tigbe, Production of human rheumatoid factors (RF) by SCID mice transplanted with synovial membrane lymphocytes, presented at the Arthritis Foundation Fellows Conference, Amelia Island, Plantation, Florida, December 8-10, 1989.

Guldner, et al., The Journal of Immunology Vol. 141, No. 2, pp. 469-475 (July 15, 1988).

Schaack, pp.585-588, In Annals of Internal Medicine Vol. 111, No. 7, pp.581-591 (October 1, 1989).

Scofield and Harley, Proceedings of the National Academy of Sciences U.S.A. Vol. 88, pp. 3343-3347 (April 15, 1991).

Remarks

The following publications describe the diagnosis of systemic lupus erythematosus and vesicular stomatitis.

U.S. patent number 4,865,970 discloses an immunometric assay that detects autoantibodies to ribosomal proteins found in the biological fluids of some systemic lupus erythematosus (SLE) patients. No method is disclosed for determining the etiological agent responsible for the expression of the autoantibodies based on sequence homology or antigenicity.

Ferris and Donaldson, Vet. Microbiol. 18: 243-258 (1988), describe an indirect, sandwich enzyme-linked

immunosorbent assay (ELISA) developed for the laboratory diagnosis of vesicular stomatitis (VS) in domestic animals. The disclosed assay uses a viral extract as the antigen. There is no selection of an antigen based on a correlation between sequence homology and antigenicity.

The following publications generally describe the reconstitution of a functional human immune system in mice with severe combined immunodeficiency (SCID).

Mosier, et al., Nature 335: 256-259 (1988), report that the injection of human peripheral blood leukocytes (PBLs) can result in the stable reconstitution of a human immune system in SCID mice.

In a presentation to the Oklahoma Lupus Association, Inc. on September 1, 1989, Dickey disclosed the production of human autoantibodies by SCID mice that had undergone successful lymphoid grafting of PBLs from patients with autoimmune disease. A short Abstract was distributed at the meeting but a copy is not presently available. The presentation schedule is enclosed. A key point of the talk was the number of cells that had to be infused into the mice in order to result in autoantibodies, which was higher than the number used simply to graft human cells into SCID mice.

Tigbe, et al., presented a paper entitled Production of human rheumatoid factors (RF) by SCID mice transplanted with synovial membrane lymphocytes to the Arthritis Foundation Fellows Conference on December 8-10, 1989. The presentation described the use of xenografts to study the production of human rheumatoid factors in SCID mice.

Guldner, et al., J. Immunol. 141: 469-475 (1988), disclose the localization of amino acid sequences within an

endogenous protein that are reactive with human autoantibodies. However, there is no correlation of sequence homology and antigenicity of the localized antigenic sequences, nor comparison of the reactive antigenic sequences with sequences of other proteins.

Schaack, Ann. Intern. Med. 111: 585-588 (1989), reports the use of computerized searches to identify homologous sequences in both a bacterial protein and an autoantigen. However, since the author does not determine the antigenicity of the identified homologous sequences, he has no way to evaluate their importance in inducing autoantibody production.

The following article was published after the filing date of the parent application.

Scofield and Harley, Proc. Natl. Acad. Sci. U.S.A., 88: 3343-3347 (1991), describe the use of the claimed method for identifying etiologic or antigenic agents responsible for the production of autoantibodies in autoimmune diseases. Utilizing this methodology, the authors propose that the etiologic agent for several autoantibodies characteristic of SLE may be a virus highly homologous to the Indiana strain of the vesicular stomatitis virus. The Examiner's attention is drawn to the art cited by the authors.

While this statement includes all of the relevant art presently known to the applicant, it should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exists. Moreover, the applicant invites the Examiner to make an independent evaluation of the cited art to determine its relevance to the subject matter of the present

application. Applicant is of the opinion that his claims patentably distinguish over the art referred to herein, either alone or in combination.

Respectfully submitted,

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Dated: July 13, 1992

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CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: July 13, 1992

Patrea L. Pabst